THE JOURNAL OF INVESTIGATIVE DERMATOLOGY
Vol. 60, No. 6

Printed in U.S.A.

THE CHEDIAK-HIGASHI SYNDROME AND THE HOMOLOGOUS TRAIT IN ANIMALS*

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INTRODUCTION

The Chediak-Higashi syndrome (CHS) is included in a symposium on genetics and the skin because of the unusual pigmentary dilution that is a primary phenotypic manifestation of the condition. Although the syndrome is rare in man, it can be investigated in several animal homologues. The disease states, which are a part of the syndrome, fascinate investigators of host defenses against infections and malignancy, and the nature of the subcellular morphologic defect offers considerable challenge to those interested in cytoplasmic organelles.

Several reviews of the condition (Windhorst et al., 1968a; Padgett, 1968; Padgett et al., 1970) have prompted this discussion which will focus on two areas that warrant further comment: the pigmentary anomaly and possible explanations for the susceptibility to infectious agents. First, a brief description of the syndrome.

THE CLINICAL STATE

Early Findings

Children brought in for treatment of CHS are generally thought by the physician to have some innocuous infection. Only if the pigmentary abnormality is recognized is the true gravity of the syndrome realized. Higashi (1954) mentioned that the mother of his patient recognized the dire prognosis on the basis of her experience with three previous siblings who had had the same unusual color. Thus, the pigmentary anomaly in all four children alerted Higashi to the possibility that the children were manifesting not just a series of multiple infections but a familial trait. This same factor may have contributed to the prominence of early reports from countries with populations consisting of rather uniformly dark-skinned individuals. Since the CHS pigmentary defect is a regular dilution of other pigment factors rather than a total absence of color, it can be missed in a child of more heterogeneous pigmentary background unless the physician thinks in terms of the individual patient's familial pigmentary constitution (Windhorst, 1968). In any event, although the early descriptions by Beguez-Cesar (1943) and Steinbrinck (1948) included the pigmentary defect as a component of the problem, Chediak (1952) and particularly Higashi (1954) arrived at the synthesis of familial pigmentary anomaly, susceptibility to infection, morphologic anomalies in the neutrophils, and early death as an entity to which Higashi's mentor, Sato (1955), ultimately appended the eponym.

Large Granules in Blood Smears

Well before the current understanding of lysosomes and the theories of storage diseases, Higashi had titled his paper, almost prophetically, "Congenital Gigantism of Peroxidase Granules." This title has stood the test of time; histochemical studies of the giant granules in blood and bone marrow preparations (Bessis et al., 1961; Mauri and Silingardi, 1964) showed them to be enlarged versions of the usual granulation for a given cell type rather than an accumulation of uniformly staining material.

Poor Prognosis for Human CHS

Children with CHS may not manifest their susceptibility to the disease for some years, but once they do, the downhill course to death, though variably prolonged, is usually inevitable. Ironically, these children are capable of making normal antibodies, developing competent delayed hypersensitivity, and handling the usual childhood viral infections.

The accelerated phase of CHS is characterized by a lymphoreticular infiltrative process which responds to the administration of steroids and antimitotic chemotherapy. Dent et al. (1966) feel these characteristics warrant applying the term malignant to the infiltrate. Ultimately the bone marrow fails and the child dies, usually of a combination of overwhelming sepsis and a hemorrhagic tendency related to the lack of neutrophils and platelets. During the course, besides hepatosplenomegaly related to the lymphoreticular infiltrate, there may be peripheral neuropathies, apparently related to the involvement of the nerves with either the genetic defect, the infiltrates, or both (Lockman et al., 1967; Sung et al., 1969).

ANIMAL HOMOLOGUES AND GENETICS

The animal models for CHS include the Aleutian trait in mink (Leader et al., 1963) and a similar mutant in Hereford cattle (Padgett et al., 1964) (Fig. 1). A carefully documented mutant of C57Bl mice, known as beige, has also been described as morphologically homologous (Lutzner et

This work was supported in part by an American Cancer Society Faculty Scholar Award (DBW) and National Institutes of Health Grants CA 05887, AI 06591, and AI 06477.

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al., 1967; Bennett et al., 1969), and preliminary evidence suggests that these animals also show increased susceptibility to infection if challenged in carefully controlled experiments (Padgett et al., 1970). Breeding experiments in all three animal models have shown them to be the results of the homozygous recessive state of an autosomal gene. All available evidence, including several reports of consanguinity (Kritzler et al., 1964) and one extensive family pedigree (Sadan et al., 1965), indicates that the human condition is also an autosomal recessive.

The animal homologues not only manifest various degrees of the clinical disease states but also offer the opportunity for epidemiologic study and controlled investigation by inoculation experiments. Padgett et al. (1970) have reviewed and summarized the results of such studies and have stated that in large mink colonies and small cattle herds the CHS animals show an increased morbidity and mortality to many different bacteria and that the Aleutian mink are more susceptible to infection, morbidity, and death from the Aleutian disease (AD) virus even though the titer of AD virus in the peripheral blood is not significantly different from that in other strains of mink. Padgett et al. (1967) have also reviewed and compared the pathologic findings in the animal homologues with those in the human condition (Table).

GIGANTISM OF CYTOPLASMIC ORGANELLES

Their Nature and Distribution

From the time of the earliest reports, the morphologic abnormality of circulating leukocytes was suspected of being related to the clinical difficulties with infectious agents and with terminal marrow failure experienced by these patients. Extensive histochemical studies indicated that abnormally large granules contain essentially the same materials as the normal granules characteristic of a non-CHS person. In an extensive ultrastructural investigation of the mink model, Lutzner et al. (1965) demonstrated that giant granules were found in practically all tissues that produce single-membrane-limited cytoplasmic organelles. Miscellaneous studies of human tissues corroborate this finding (Kritzler et al., 1964; Windhorst et al., 1968a). Thus, it appears that this single gene defect influences the basic structure, though not necessarily the contents, of a wide variety of cytoplasmic granules throughout the body.

Origins

Davis et al. (1971a, b) have used the electron microscope to study the evolution of abnormal granules in the precursors and mature cells of mink bone marrow. They found that the neutrophil precursors of mink resemble those of rabbits in which at least two different types of granules are thought to arise from opposite sides of the Golgi apparatus (Bainton and Farquhar, 1966, 1968a, b). In the Aleutian mink, the primary or azurophil granules were abnormal in size and structure in the early phases, and the giant forms of the mature neutrophils developed from the fusion of these abnormal precursors. The secondary or "specific" granules, on the other hand, appeared to arise normally and to remain uninvolved in the generation of giant granules. Thus, only one of the subclasses of granules seen in normal neutrophils (Baggiolini et al., 1969) participated in the genetic abnormality. Little is known about such subpopulations in any cells except polymorphonuclear leukocytes. As information about the origins of other granules is reported, it should be interesting to see whether the CHS adds to our understanding of variations in cytoplasmic organelles. Davis et al. (1971b) found what appear to be two subclasses of granules in the mink basophils, but only one type, all abnormal, in the eosinophils. White (Windhorst et al., 1968a), on the other hand, has photographs of human CHS eosinophils that suggest a varied granule constitution.

Attempts to Isolate Granules

Windhorst et al. (1968a), using a sucrose density gradient in a zonal ultracentrifuge, attempted to isolate the giant granule fraction from the livers of Aleutian mink. The results suggested that the large granules are highly susceptible to rupture by the simplest of tissue homogenization procedures, which resulted in relatively increased amounts of soluble lysosomal enzymes in the gradients from abnormal livers compared with those from non-Aleutian controls. Padgett's group, using different techniques for cell rupture, were also unable to isolate enlarged CHS mink neutrophil granules (Padgett, G. A., unpublished data).

Role of Membranes

A major question in CHS is whether the giant granules are formed by the failure of some primary mechanism that controls the size of such organelles or by the fusion of granules that are of normal size when first formed. Neither possibility necessarily excludes the other, but because of the widespread nature of the defect a definite answer would have important implications: whichever process is at work, it is common to many if not all cells. Detection of a defect in the membrane surrounding the organelles could provide an answer that would supersede both the other alternatives. Since membranes are composed of both lipid and protein, a defect in protein structure would be a direct reflection of the mutant gene, whereas a defect in lipid composition would require a more complex analysis. Methodologies for investigating membranes are difficult, but some information about those of CHS is available.

The incorporation of P^{32} in the cellular phospholipid of resting and active phagocytes was normal in CHS mink and cattle (Page and Pad-

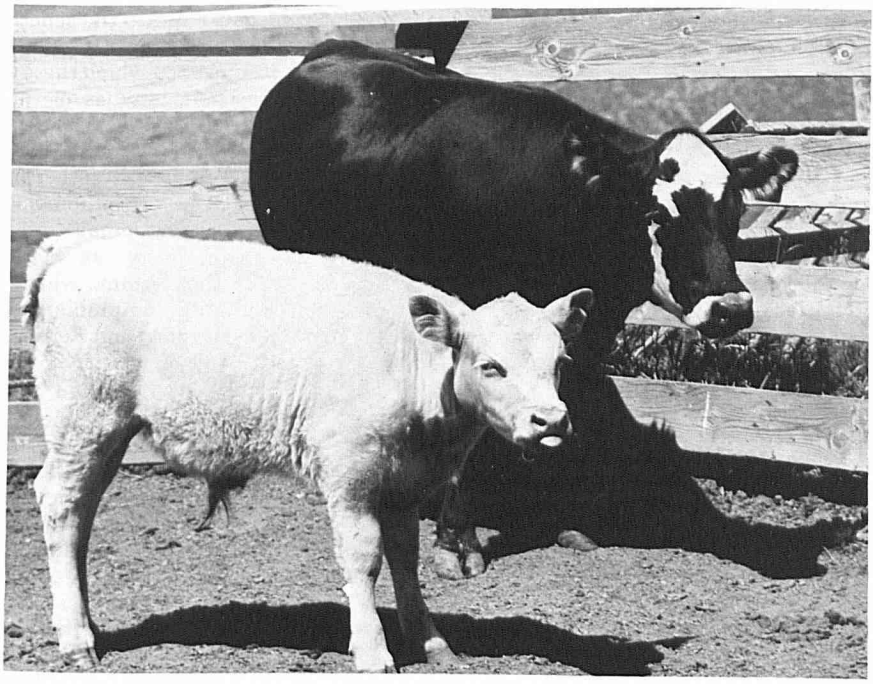

FIG. 1. A CHS Hereford calf with its mother to illustrate the color dilution in this strain of basically red-haired animals. The dilution is associated with susceptibility to disease, giant cytoplasmic organelles, and early death. Transmission is autosomal recessive.

TABLE

Comparative aspects of the Chediak–Higashi syndrome of man, mink, cattle, and mice

Characteristic	Man	Mink	Cattle	Mice
Autosomal recessive mode of inheritance	yes	yes	yes	yes
Clinical Studies				
1. Increased susceptibility to infection	yes	yes	yes	yes
2. Similar distribution of enlarged granules	yes	yes	yes	yes
3. Similar morphology of enlarged granules	yes	yes	yes	yes
4. Similar histochemistry of enlarged granules	yes	yes	yes	yes
5. Bleeding tendency	yes	yes	yes	yes
6. Similar inflammatory response	yes	yes	yes	?
7. Immunologic deficiency	no	no	no	?
8. Pigmentary dilution	yes	yes	yes	yes
9. Accelerated phase	yes	no	no	no
10. Elevated muramidase levels	yes	no	no	no
Experimental Studies				
1. Delayed chemotaxis in vitro	yes	yes	?	yes
2. Decreased serotonin levels	yes	yes	yes	yes
3. Virus-like particles observed	occasional	no	occasional	no
4. Sequestration vacuoles observed	occasional	no	no	no
5. Abnormal serum lipid pattern	yes	no	no	no
6. Autophagy	occasional	no	no	no
7. Abnormally fragile enlarged granules	yes	no	no	no
8. Abnormal bactericidal capabilities of neutrophils	±	±	no	?
9. Abnormal membrane permeability	occasional	no	no	?
10. Decreased renal tubular catabolic function	?	yes	?	yes

gett, unpublished data); whereas Kanfer et al. (1968) found an accelerated rate of phospholipid turnover in the form of sphingomyelin in CHS patients. Windhorst (unpublished data) found that the incorporation of C^{14} labeled inositol into the phospholipids generated by enzymes from the liver homogenates of Aleutian mink was normal. Holland (1970) found no difference between nor-

mal cells and the red cells of the mutant cattle in fragility, total lipids, electrophoretic distribution of phospholipids, amino acid composition, and insoluble protein component.

Page et al. (1962) found that blood 5-hydroxytryptamine levels were low in two patients, suggestive of a defective platelet binding capacity for serotonin. More recent observations by Holland in Padgett's group indicate that platelet serotonin is almost unmeasurable in mutant mink, cattle, and mice and that added serotonin is not stored by the abnormal platelets as effectively as by normal ones. However, Davis et al. (1971b) found that the granules of Aleutian mink platelets are morphologically normal.

THE PIGMENT ANOMALY IN CHS

The color defect seen in CHS affects the skin, hair, and eyes. A number of casual descriptive terms have been applied to this phenomenon, e.g., partial albinism, oculocutaneous albinism, and semialbinism. However, since our information on the basic mechanisms of pigmentation has become increasingly more complete, our understanding of classical albinism has reached the molecular level and we are forced to be more precise in our use of such terms. Such preciseness is especially important since these terms have rather specific implications in clinic evaluations.

The Melanosome as a Particular Cytoplasmic Organelle (reviewed in Fitzpatrick et al., 1971a)

The origin of color in the skin, hair, and eye of mammals derives principally from the melanosome, a special single membrane-bound cytoplasmic organelle produced by melanocytes. The pigment it produces, melanin, is a highly insoluble, electron-dense hydroquinone able to absorb light across the entire visible spectrum with no characteristic absorption peaks. It is laid down on the melanosome by the action of a copper-containing enzyme, tyrosinase, which is apparently incorporated into the developing membrane structure of the immature melanosome as it is formed in the endoplasmic reticulum and the Golgi apparatus (Seiji, 1967). Several subvarieties of melanin and at least two types of tyrosinase, all under distinct genetic control, account for the different colors. In addition, the availability of the substrate amino acid, tyrosine, to this system may depend on genetically determined carrier molecules.

The color of the epidermis and of the hair shaft arises from the secretion of melanosomes into the developing keratinocytes and hair matrix cells. The size and number of the melanosomes affect the final hair color; in addition, the shape may be reflected in subtle variations in color. These aspects are also under genetic control (Moyer, 1966). Inhibitors of melanin formation in the melanocyte (Halprin and Ohkawara, 1967) and the way in which the keratinocyte does or does not "package" the melanosome play a role in the genetics of racial color (Szabo et al., 1969).

Many of the results upon which these statements are made are based on studies of inbred mice, where at least 70 genes at 40 loci influence the color of the animal (Wolfe and Coleman, 1966). Generalizing from such information to other animal species is warranted by the fact of homologous structures and defects among mammals (e.g., tyrosinase deficiency in true albinism) as well as by the ancient nature of the system, which is clearly present in birds, reptiles, amphibians, and fish as well as mammals (Bagnara and Ferris, 1971).

The CHS Melanosome

Since the chemical nature of melanin is such that it is naturally electron-dense, ultrastructural observations on the pigmentary abnormality in CHS may be somewhat more significant than those derived from cells whose organelles not only must be fixed externally but also contain high concentrations of lysosomal enzymes, e.g., neutrophils.

Windhorst et al. (1966) have shown that the early melanosomes of human CHS are sometimes extremely large, even though the lamellated membrane substructure may appear to be quite orderly (Fig. 2). In addition, the pattern of the membranes of maturing CHS melanosomes, evidenced by increasing melanization, suggests some fusion of smaller forms. On the basis of these findings and the demonstration of adequate tyrosinase activity in the epidermal melanocytes of the patient, Windhorst et al. (1968b) proposed that CHS represents a human pigmentary dilution based on a primary alteration of the structure of melanosomes. With material from the same patient, Zelickson et al. (1967) showed that the destruction of the melanosomes in the keratinocytes may be acclerated in CHS.

Giant melanin granules present in animal homologues are a necessary consideration in defining CHS. In a serial study of the eye of the developing fetal beige mouse, Lutzner (1969) found abnormally large melanin granules in both the retina, which contains melanocytes derived from the optic cup, (Moyer, 1961) and the choroid, which, like all cutaneous melanocytes, is neural crest in origin. This difference was evident in the earliest fetuses in which premelanosomes could be detected. Moreover, these early giant granule membranes were disrupted and the melanosome fibers were surrounded by vacuolar spaces. Both the retina and the choroid as well as the pia arachnoid of human patients have been shown to contain melanized but giant melanosomes (Windhorst et al., 1968b; Bedoya et al., 1969).

The Pigmentary Dilution of CHS

When the effects of these subcellular variations are observed in the intact model, a partial dilution of the basic color constitution of the individual

FIG. 2. Electron micrograph of melanocyte from hair follicle of CHS patient. Early melanosomes of normal but giant substructure plus evidence for fusion of giant forms are present. (Osmium fixed, epon embedded, uranyl acetate stained, about × 31,000). (Reproduced from Windhorst, D. B., Zelickson, A. S., and Good, R. A. 1966. Chediak-Higashi syndrome: Hereditary gigantism of cytoplasmic organelles. Science, *151*:81–83. Copyright 1966 by The American Association for the Advancement of Science.)

results. This is particularly evident in the mink in which careful breeding accomplishes exactly this effect; the resulting series of colors are known as the "blues" (Shackleford, 1950). Another important corollary is that a basically dark individual will still be dark and his eye color will correspondingly range from brown (in a child of dark-eyed heritage) to the translucent "albino" eyes in a person whose "color base" is quite light. Photophobia and nystagmus are present even when the eyes show substantial color (Bedoya et al., 1969).

Clinically, the term partial albinism has come to be associated with piebaldism, a genetically determined localized absence of melanin-forming cells equivalent to spotting in mice. Oculocutaneous albinism has come to mean the lack of melanin-forming capacity with subdivisions relating to the presence or absence of tyrosinase activity in the melanocytes (Fitzpatrick and Mihm, 1971; Fitzpatrick et al., 1971b). This abnormality is fully homologous to the albinism observed in lower forms, including mice and mink, which in these species is at a different genetic locus from that of CHS.

Thus, none of the terms commonly used to describe the pigment in CHS convey the full implications about (1) the genetic specificity of the trait, (2) its unique effect on the structure of the subcellular organelle carrying the pigment, (3) the particular bluish effect on the observed color, sometimes even relatively mild in degree, which this conveys, or (4) the special implications of this particular melanosomal abnormality on the interrelationships of pigment-forming cells with other cells of the body, particularly the circulating granulocytes.

DEFECTIVE DEFENSE MECHANISMS IN CHS

General Comments

In all the homologues studied, CHS correlates with a lowered capacity to deal with various infectious agents, including bacteria, viruses, and fungi (*Candida albicans*). This seems to be a nonspecific phenomenon in the intact host; that is, where epidemiologic studies have been made, Aleutian mink respond to all bacterial and some viral agents with increased morbidity and mortality. On the other hand, the possibility that a particular virus, e.g., infectious mononucleosis or viral hepatitis, is responsible for the ultimate lymphoproliferative disease in the children has not been ruled out, and these syndromes are mentioned in several reports as being related to the onset of the accelerated phase of the condition. In addition, there is the unusual syndrome, Aleutian disease (AD) seen in Aleutian mink affected by a particular virus (Henson et al., 1966).

Studies on children (Page et al., 1962) and animals (Leader et al., 1963; Levine et al., 1966) have demonstrated a normal capacity to form antibodies and to develop delayed hypersensitivity. These findings, combined with the morphologic abnormalities of granulocytes and with the development of new abilities to evaluate phagocytes, have led to an intensive examination of the functional capacities of the neutrophil in CHS. It will be useful to report these studies in a way that will relate them to a systematic understanding of normal phagocyte function.

Normal Phagocyte Functions and Methods for Their Evaluation

Figure 3 (from Windhorst and Katz, 1972) is adapted from a more detailed analysis of the basic methodology for studying phagocytes which has, in turn, been adapted for the study of clinical states (Windhorst, 1970). The discovery and detailed analysis of a prototype defect in intracellular phagocytic function, chronic (fatal) granulomatous disease of childhood (CGD) (Good et al., 1968) have greatly stimulated interest in these important components of innate defense.

Although Windhorst (1966), Windhorst et al. (1968a), and Padgett (1967) were unable to detect an abnormality in human, mink, or cattle CHS leukocytes similar to that in CGD, their results were preliminary, and as will be seen below, have been superseded. The recent work on CHS will be discussed according to the separate compartments of Figure 3.

Maturation and Circulation of Neutrophils in CHS

Blume et al. (1968) in a difficult study of CHS patients, found that hypersplenism is often present when the child is sick, but if it is not, the neutrophils have a normal half-life in the peripheral circulation. They also found increased levels of serum muramidase (lysozyme) and the lack of a leukocytic response to etiocholanolone. These findings were taken to indicate an increased destruction of the precursors of granulocytes within the marrow before they were released into the circulation. Padgett et al. (1970) found that cattle and mink do not have increased levels of serum muramidase and that the levels of circulating granulocytes in CHS and normal animals were not different. In addition, Eklund et al. (1968) found that leukocyte levels both in CHS mink with AD and in normal mink with AD were normal.

Kanfer et al. (1968) interpreted their finding of increased leukocyte sphingolipid turnover as compatible with increased lability of these cells which a rapid bone marrow turnover would suggest. Both papers are compatible with White's findings (1966, 1967) of increased cytoplasmic autophagy in human leukocytes and Windhorst et al.'s (1968a) report of the probable lability of mink liver lysosomes in CHS.

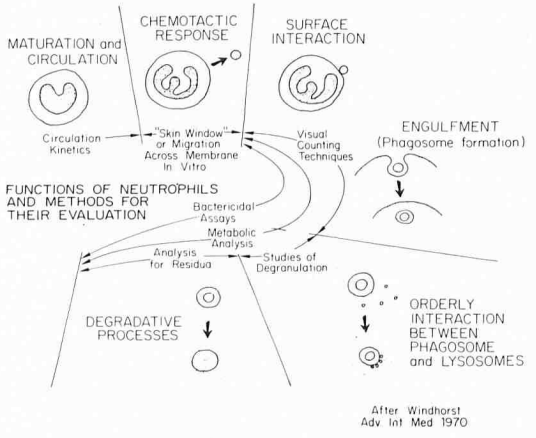

FIG. 3. Simplified diagram of the various parameters of phagocyte function for which methodologies are available for study. The rapid evolution of this type of work in clinical medicine relates to the discovery of chronic granulomatous disease of childhood, an X-linked defect in the intracellular events portrayed in the last two segments of the diagram. As indicated in the text, CHS has defects in various degrees in the first two components as well as the last two aspects of phagocyte function. (From Windhorst and Katz, 1972, by permission).

Chemotactic Responses

Despite an early report by Page et al. (1962) that in vivo skin-window studies do not reveal abnormal cell migration (Windhorst et al., 1968a), Clark and Kimball (1970) and Clark et al. (1971) have found that when exposed to standard chemotactic stimuli, the granulocytes of human and mink CHS are definitively abnormal in their capacity to migrate in vitro in a Boyden chamber. There was no defect in the ability of CHS serum to generate chemotactic factors.

Surface Interaction, Engulfment, and Degranulation

The reports of Page et al. (1962) and Saraiva et al. (1959) on opsonic indices, as well as the quantitative bactericidal studies reported below, indicate that the uptake of bacteria by CHS leukocytes is not defective when adequate amounts of normal or CHS serum are present. Padgett (1967) and Root et al. (1968) have found that the abnormally large PMN granules fail to fuse with phagosomes whereas normal granules function properly. Padgett et al. (1970) suggest that this is evidence for an abnormal stability of the giant granular membrane rather than an increased lability suggested by White (1967).

Intracellular Bacterial Killing and Degradation

Root (1971), Stossal et al. (1972), and Root et al. (1972) have studied human CHS extensively for phagocytic uptake and other functions, utilizing various organisms in the quantitative bactericidal tests and analyzing metabolic activity as well. They find that the kinetics of the ability of CHS phagocytes to kill organisms is such that a defect can be detected for *E. coli* and *C. albicans* only at a

time interval of 20 minutes, whereas the abnormal killing of *Staph. aureus*, D-streptococcus, and a rough strain of pneumococcus can be seen up to two hours, but not later. They interpreted their results to indicate that the early defect in bacterial killing is a consequence of the slow-to-absent fusion of the peroxidase-containing giant granules with the phagosome and raised the possibility that this fusion is important in the early kinetics of normal phagocytic killing. Davis (1970) found CHS cattle leukocytes deficient in bactericidal capacity.

In this same general category, though not strictly involving the phagocytic system associated with defense against infections, Prieur and Padgett (1970) and Prieur et al. (1972) have shown that the proximal convoluted renal tubules of CHS mink and mice handle an intraperitoneal dose of horseradish peroxidase differently from and more slowly than normal mink kidneys. They suggest that an understanding of this finding will contribute to our knowledge of the genesis of the lupus erythematosus-like glomerulonephritis seen in Aleutian disease. In addition, it may correlate very well with the delayed fusion of granules that has been observed in the neutrophil.

CONCLUSION

The Chediak–Higashi syndrome seems to represent a defect in subcellular structure which in turn is reflected in functional abnormalities of seemingly diverse cell lines. This correlation is, of course, not surprising in view of the many metabolic features shared by all mammalian cells. However, the single membrane-bound cytoplasmic organelles can legitimately be regarded as distinctive for the cell in which they occur, that is, they express specifically the full differentiative capacity of any given cell, be it neutrophil or melanocyte. In this sense, such structures could be expected to express the unique characteristics of the differentiation of a given cell. The Chediak-Higashi syndrome indicates that not all the characteristics of such granules are unique, but at least one feature under genetic control is common to most if not all such organelles.

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